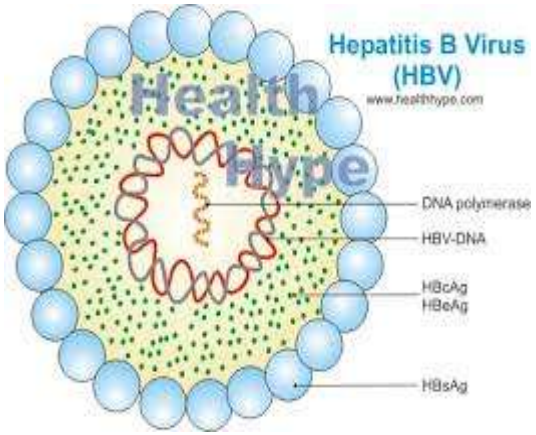
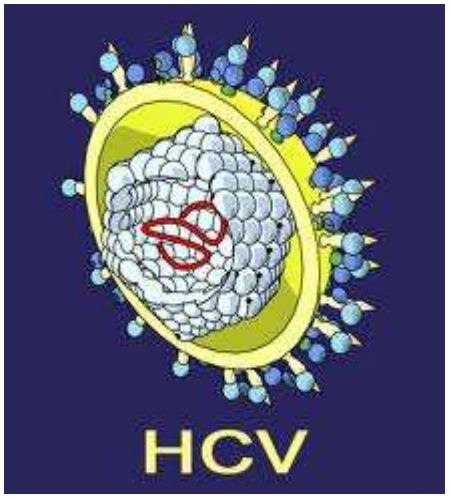
Viral Hepatitis Induced Glomerulopathy: Debates On Renal Biopsy And Management



By

Alaa Sabry., MD



Road map of the presentation

- HCV associated Nephropathy.
  - Pathogenesis.
  - Glomerular lesions.
  - Therapy.
- HBV associated Nephropathy.
  - Pathogenesis .
  - Glomerular lesions .
  - Therapy.

MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS ASSOCIATED WITH HEPATITIS C VIRUS INFECTION

RICHARD J. JOHNSON, M.D., DAVID R. GRETCH, M.D., PH.D., HIDEAKI YAMABE, M.D., JAIME HART, B.S., CARLOS E. BACCHI, M.D., PH.D., PETER HARTWELL, M.D., WILLIAM G. COUSER, M.D., LAWRENCE COREY, M.D., MARK H. WENER, M.D., CHARLES E. ALPERS, M.D., AND RICHARD WILLSON, M.D.

Abstract *Background and Methods.* Hepatitis C virus (HCV) infection causes both acute and chronic liver disease and is also associated with mixed cryoglobulinemia. Whether HCV is also associated with renal disease, as is the hepatitis B virus, is not known. We describe the clinical, pathologic, virologic, and immunologic features of eight patients with HCV infection who were referred to nephrologists for glomerulonephritis. Four patients were treated with interferon alfa.

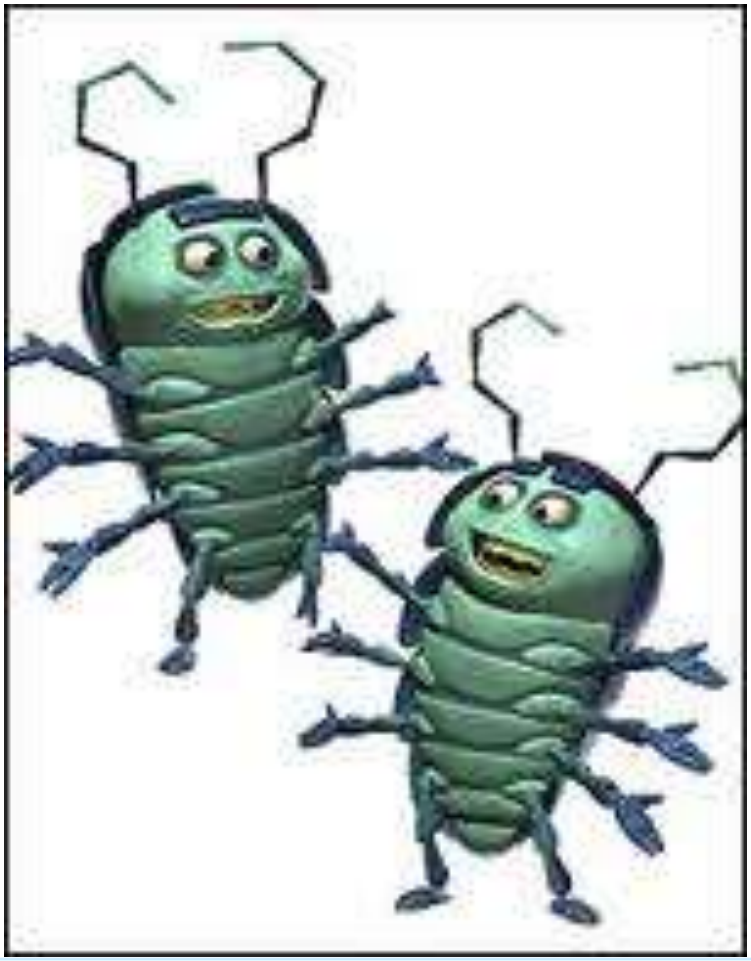
Results. All eight patients had proteinuria, and seven had decreased renal function. Renal biopsy in all patients revealed membranoproliferative glomerulonephritis, characterized by the deposition of IgG, IgM, and C3 in glomeruli. Electron microscopy of the biopsy specimens showed cryoglobulin-like structures in three of four patients. All eight patients had HCV RNA detected in their serum, elevated serum aminotransferase concentrations, and hypocomplementemia, and the majority had cryoglobulins and circulating immune complexes in their serum. Cryoprecipitates from the three patients who were tested contained HCV RNA and IgG anti-HCV antibodies to the nucleocapsid core antigen (HCVc or c22-3). IgM rheumatoid factors, present in all patients, bound anti-HCV IgG in all six patients tested. Four patients received interferon alfa for 2 to 12 months; all had evidence of decreased HCV replication and improvement of their renal and liver disease.

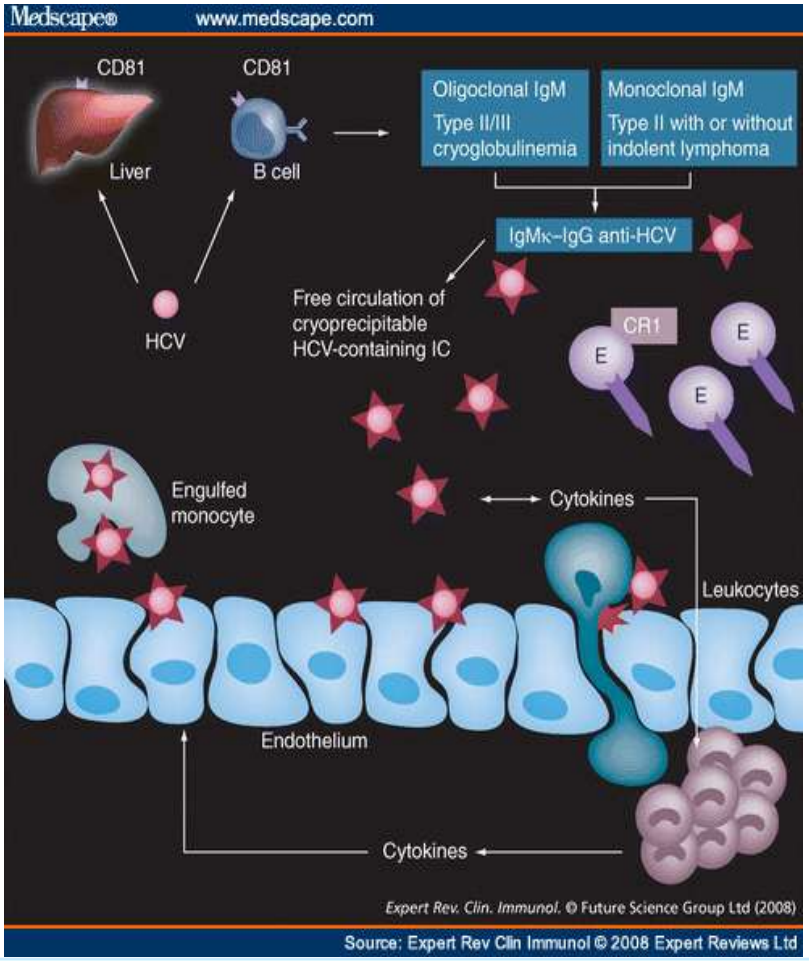
Conclusions. Chronic HCV infection is associated with cryoglobulinemia and membranoproliferative glomerulonephritis. The pathogenesis is unknown, but may relate to deposition within glomeruli of immune complexes containing HCV, anti-HCV IgG, and IgM rheumatoid factors. (N Engl J Med 1993;328:465-70.)

These observations were subsequently confirmed by hundreds of studies all over the world, thereby revealing that the majority of patients with type II mixed essential cryoglobulinaemia were, indeed, victims of HCV infection.

HCV associated Nephropathy. Pathogenesis

Immune Response





It is not the bug that kills you; it makes you kill yourself

2- Direct Cytopathic Effect

- The virus has the theoretical potential to cause renal injury by a number of direct mechanisms :
- The kidney is perfectly qualified to be a target for HCV infection :
- It has the cell surface molecules (*CD81 and SR-B1 receptors)* required for adhesion , entry (e.g. C1q, TLR-3) are abundantly expressed in the renal parenchymas
- Viral replication has been documented in the renal tubules in patients with HCV-associated interstitial nephritis
- Many of the ingredients required for HCV attachment (e.g. glycosaminoglycans)
- it may be speculated, though yet unproven, that the virus has the potential of entry and replication in renal tissue if conveyed by infected B-lymphocytes .
- Sporadic reports suggest that replication may also occur in other sites such as the renal tubules .

(Kasuno K, Ono T, Matsumori A et al. Am J Kidney Dis 2003; 41: 767–775)

- HCV-related granular protein deposits located in the mesangium were found to be related to higher degrees of proteinuria.

(Rodríguez-Iñigo E et al., *J Viral Hepat 2000; 7: 23-29*)

3-Hepatic injury

- Decreased clearance of circulating immune complexes,
- Decreased synthetic function for numerous serum proteins, and hemodynamic perturbations, with known or potential consequences for the kidney.

Biopsy

- Membranoproliferative glomerulonephritis .
- Membranous nephropathy .
- Focal Segmental Glomerulosclerosis.
- Fibrillary glomerulonephritis.
- Immunotactoid glomerulopathy.
- IgA nephropathy.
- Renal thrombotic microangiopathy.
- Vasculitic renal involvement .
- Interstitial nephritis.

(Abdullah Ozkok, and Alaattin Yildiz., *World J Gastroenterol 2014 : 20(24): 7544-7554)*

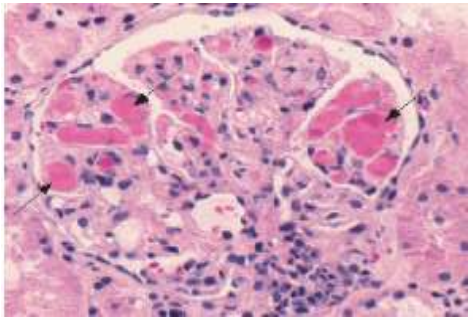
Nephrol Dial Transplant (2002) 17: 239–245

Nephrology Dialysis Transplantation

Original Article

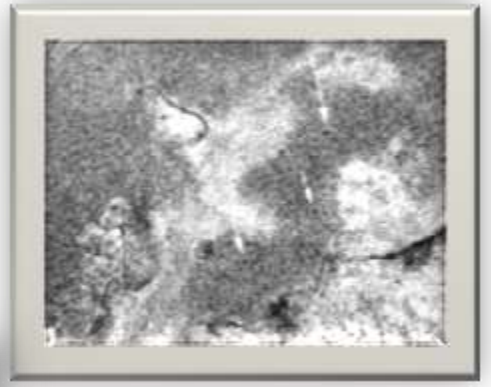
A comprehensive study of the association between hepatitis C virus and glomerulopathy

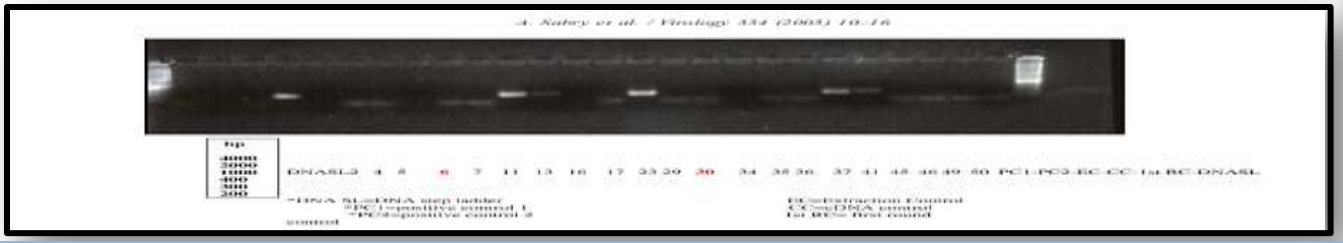
Alaa A. Sabry[1,2], Mohamed A. Sobh[2], William L. Irving[3], Anna Grabowska[3], Bart E. Wagner[4], Samantha Fox[5], Gura Kudesia[5] and A. Meguid El Nahas[1]



Light microscopic :

- Endocapillary proliferation
- large eosinophilic and PAS-positive intraluminal Thrombi
- Diffuse, mesangial expansion and hypercellularity with capillary loop thickening
- Double contours of BM caused by the interposition of monocytes between the basement membrane and the endothelium.





There is a strong causal association Between HCV and MPGN

Membranous glomerulonephritis

- **Several small studies have suggested that membranous nephropathy may be induced by chronic HCV infection, although the data are conflicting.**

  (Johnson R et al. Kidney Int 1994, Johnson RJ, et al 1993 NEJM : 328:465)

- **the prevalence of membranous nephropathy was significantly higher in HCV-positive compared to HCV-negative renal transplant patients .**

- (Morales JM, et al. Transplantation 1997;63:1634)

- **A Japanese group detected HCV core protein in the glomeruli .**

  (Okada, K,. Clin Nephrol 1996; 45:71)

- **These findings support a possible pathogenic role of HCV in the development of MGN.**

- However, in a study of 19 patients with membranous nephropathy, only one (5 percent) had anti-HCV antibodies, which was not different from that observed in control patients with diabetic nephropathy.

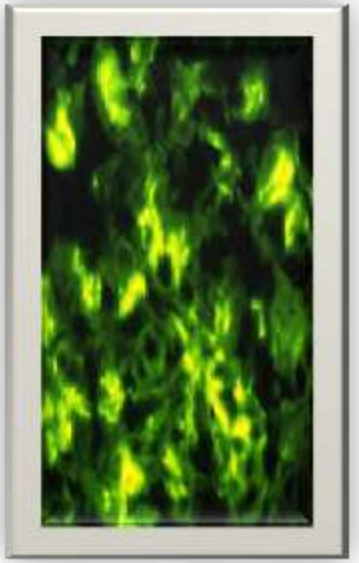
  (Cosio FG, et al. Am J Kidney Dis 1996; 28:752).

- The biopsy features of MGN in patients with HCV infection are similar to those of idiopathic MGN.
- Usually serum complement levels are normal , cryoglobulins and RF are absent in the serum.

Overall, these findings suggest but do not prove a possible role of HCV in the development of membranous nephropathy.

IgAN

- **The biopsy features of IgAN associated with HCV infection are similar to those encountered in other forms of IgAN.**
- **Circulating immune complexes containing IgA and HCV antigens have not been reported .**
- **The pathogenetic link between HCV infection and IgAN is uncertain.**



FSGS

- The development of focal and segmental glomerulosclerosis (FSGS) in patients with HCV infection has been described in several studies.

  Stehman-Breen et al. Nephron 1999;81:37-40.

- **A case was attributed by the authors to therapy withIFN-α, and the second occurred in a renal transplant recipient several decades following transplantation, a setting in which FSGS occasionally develops as a result of hyperfiltration**

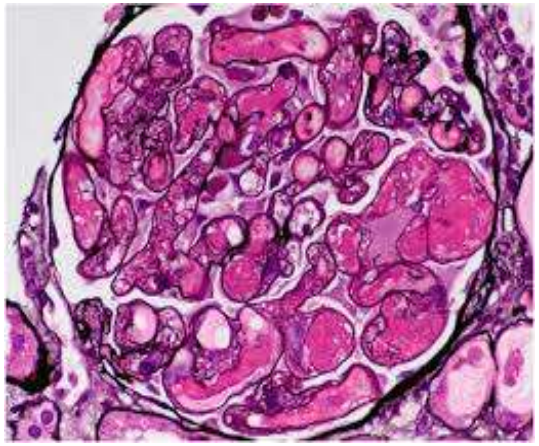
  Trimarchi HM, Gonzalez JM, Truong LD, et al.. Nephron 1999;82:270-

- The association between HCV and FSGS is therefore somewhat speculative.

Thrombotic microangiopathy (TMA)

- Has been described in occasional patients with HCV infection, including renal transplant recipients.

  (Herzenberg AM et al. Am J Kidney Dis 1998;31:521-6,
  Baid al. J Am Soc Nephrol 1999;10: 146-53) .



- The biopsy findings in this disorder are similar to those in other forms of TMA.

- Most (but not all) of the transplant recipients were being treated with cyclosporin A, a drug whose use is also occasionally associated with TMA.

- The ultrastructural findings in TMA also overlap to some extent with those of transplant glomerulopathies.

  (Miller S etal., Saudi J Kidney Dis Transplant 2000;11(2):145- 160)

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(N Engl J Med 1993;328:465-70.)

Johnson et al," *In the early 1990s, standard alpha-interferon (α-IFN) was used alone at different doses, i.e. 3 to 10 MU three times a week: It reduces proteinuria with variable effects on renal function and 2 patients relapsed after IFN therapy course . unfortunately, the results were disappointing.*

INTERFERON ALFA-2a THERAPY IN CRYOGLOBULINEMIA ASSOCIATED WITH HEPATITIS C VIRUS

ROCCO MISIANI, M.D., PIERMARIO BELLAVITA, M.D., DOMENICO FENILI, BIOL.SC.D., OMAR VICARI, BIOL.SC.D., DONATELLA MARCHESI, M.D., PIER LUIGI SIRONI, M.D., PIO ZILIO, M.D., ARIALDO VERNOCCHI, BIOL.SC.D., MARGHERITA MASSAZZA, M.D., GIOVANNI VENDRAMIN, M.D.,

THE NEW ENGLAND JOURNAL OF MEDICINE March 17, 1994

In 15 patients who had a complete clearance of HCV RNA after α-IFN therapy, an improvement in renal function was observed . However, there was no effect on proteinuria and all patients relapsed after α-IFN therapy was stopped.

Hepatitis C virus-associated glomerulonephritis. Effect of α-interferon therapy

RICHARD J. JOHNSON, DAVID R. GRETCH, WILLIAM G. COUSER, CHARLES E. ALPERS, JEFF WILSON, MINJUN CHUNG, JAIME HART, and RICHARD WILLSON

Divisions of Nephrology and Gastroenterology, Department of Medicine, and the Departments of Laboratory Medicine and Pathology, University of Washington Medical Center, Seattle, Washington, USA

14 patients were treated with α-IFN for 6 to 12 months .
Overall, proteinuria significantly decreased, while renal function remained stable.
However, virological and renal relapses were observed after completing the therapy.

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Effect of interferon-alpha-based antiviral therapy on hepatitis C virus-associated glomerulonephritis: a meta-analysis

Bo Feng[1], Garabed Eknoyan[2], Zhong-sheng Guo[1], Michel Jadoul[3], Hui-ying Rao[1], Wei Zhang[1] and Lai Wei[1]

Table 1. Characteristics of included studies

Authors	Patients, *n* (total/treated)	Country	Publication year	Study design	Lost or terminated antiviral therapy
Abbas *et al.* [25]	30/27	Pakistan	2008	Prospective, (cohort) study	3
Alric *et al.* [7]	25/18	France	2004	Prospective, controlled	0
Beddhu *et al.* [26]	17/11	USA	2002	Retrospective, controlled	0
Bruchfeld *et al.* [27]	7/7	Sweden	2003	Retrospective	1
Garini *et al.* [10]	4/4	Italy	2007	Retrospective, case series	0
Johnson *et al.* [28]	34/14	USA	1994	Retrospective, controlled	3
Komatsuda *et al.* [29]	19/5	Japan	1996	Retrospective, controlled	0
Mazzaro *et al.* [23]	13/7	Italy	2000	Case controlled	1
Misiani *et al.* [9]	53/27	Italy	1994	Prospective randomized, controlled	4
Rossi *et al.* [19]	3/3	Italy	2003	Case series	0
Sabry *et al.* [12]	20/20	Egypt	2002	Prospective	0

Authors	Antiviral agent	IFN dose	Therapy duration	Patients, *n* (SVR/no SVR)
Abbas *et al.* [25]	IFN-α + RBV	3MU 3/week, RBV 200–1000 mg/day	At least 24 weeks	4/26
Alric *et al.* [7]	IFNα (14) or Peg-IFNα + RBV (4)	3MU 3/week1.5 μg/kg/week, RBV 600–1000 mg/day	24–96 weeks	12/6
Beddhu *et al.* [26]	IFNα	3MU 3/week	48 weeks	1/10
Bruchfeld *et al.* [27]	IFNα (5) or Peg-IFNα + RBV (2)	3MU 3/week, 1.0 μg/kg/week, RBV 200–800 mg/day	Genotype 2 or 3: 24 weeks; Genotype 1: 60 weeks	5/2
Garini *et al.* [10]	IFNα + RBV (2) or Peg-IFNα + RBV (2)	3MU 3/week, RBV 15 mg/kg/day, 80–100 μg/kg, RBV 800–1000 mg/day	24–48 weeks	3/1
Johnson *et al.* [28]	IFNα	3MU 3/week	24–48 weeks	6/5
Komatsuda *et al.* [29]	IFNα	6MU 7/week	24 weeks	0/5
Mazzaro *et al.* [23]	Lymphoblastoid-IFN	3MU 3/week	24wk	1/6
Misiani *et al.* [9]	IFNα-2a	1.5MU 3/week × 1 week; 3 MU 3/week × 23 week	24 weeks	2/25
Rossi *et al.* [19]	IFNα + RBV	3MU 3/week, RBV 15 mg/kg/day	48 weeks	3/0
Sabry *et al.* [12]	IFNα + RBV	3MU 3/week, RBV 15 mg/kg/day	48 weeks	5/15

[a]RBV, ribavirin.

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Study or Subgroup	Pretreatment Mean	SD	Total	After treatment Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Alric 2004	1.98	2	18	1.1	0.9	18	25.9%	0.88 [-0.13, 1.89]
Beddhu 2002	6.5	6.1	11	2.39	1.62	11	9.0%	4.11 [0.38, 7.84]
Bruchfeld 2003	4.02	3.58	7	2.51	3.12	7	9.7%	1.51 [-2.01, 5.03]
Garini 2007	6.7	3.4	4	1.09	1.88	4	8.7%	5.61 [1.80, 9.42]
Johnson 1994	5.8	4.1	14	2	2.6	14	14.4%	3.80 [1.26, 6.34]
Mazzaro 2000	5.3	3.1	7	2.5	2.2	7	12.9%	2.80 [-0.02, 5.62]
Rossi 2003	3.47	1.59	3	0.53	0.25	3	19.4%	2.94 [1.12, 4.76]
Total (95% CI)			**64**			**64**	**100.0%**	**2.71 [1.38, 4.04]**

Heterogeneity: Tau² = 1.50; Chi² = 12.70, df = 6 (P = 0.05); I² = 53%
Test for overall effect: Z = 4.00 (P < 0.0001)

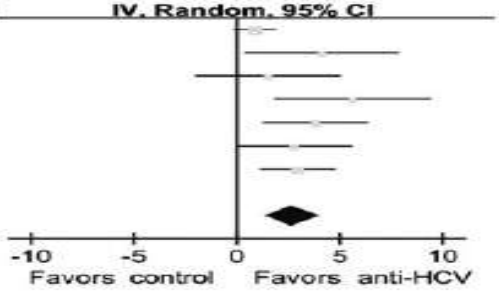

Fig. 2. Forest plot of proteinuria evolution from baseline after antiviral treatment.

IFNa can decrease protein excretion level significantly [mean difference, 2.71 g/24 h; (95% CI 1.38–4.04, P < 0.0001)]

Study or Subgroup	Pretreatment Mean	SD	Total	Posttreatment Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Alric 2004	1.33	0.46	18	1.2	0.35	18	37.5%	0.13 [-0.14, 0.40]
Beddhu 2002	1.69	0.43	11	1.58	0.53	11	21.2%	0.11 [-0.29, 0.51]
Bruchfeld 2003	3.01	2.95	7	1.92	1.26	7	0.8%	1.09 [-1.29, 3.47]
Garini 2007	1.3	0.4	4	0.5	0.58	4	8.5%	0.80 [0.11, 1.49]
Johnson 1994	2	0.7	14	1.5	0.6	14	15.8%	0.50 [0.02, 0.98]
Mazzaro 2000	1.7	0.4	7	1.7	0.5	7	16.3%	0.00 [-0.47, 0.47]
Total (95% CI)			**61**			**61**	**100.0%**	**0.23 [0.02, 0.44]**

Heterogeneity: Tau² = 0.01; Chi² = 6.05, df = 5 (P = 0.30); I² = 17%
Test for overall effect: Z = 2.12 (P = 0.03)

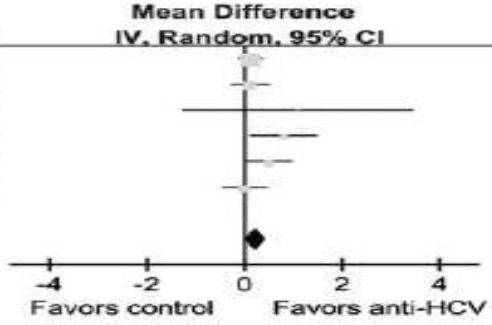

Fig. 3. Forest plot of creatinine evolution from baseline after antiviral treatment.

Serum creatinine levels also decreased significantly [mean difference, 0.23 mg/dL; (95% CI 0.02–0.44, P ¼ 0.03)] at the end of therapy

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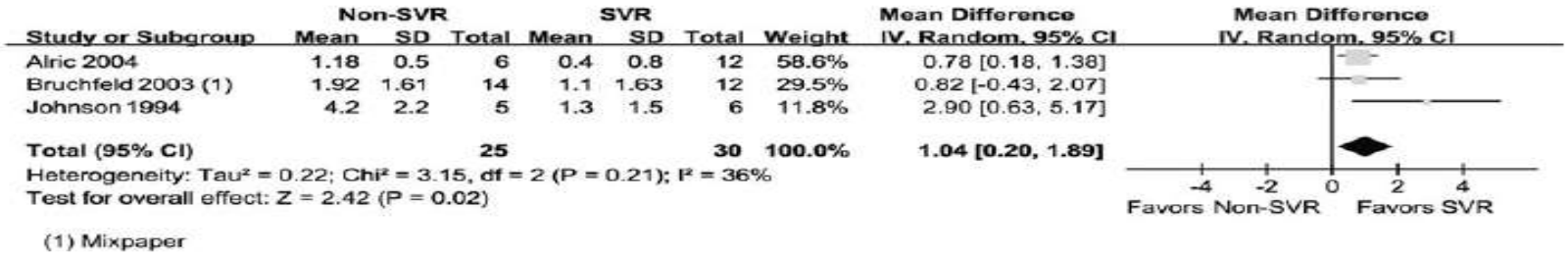

Fig. 4. Forest plot of the comparison of proteinuria evolution between patients with SVR and those with non-SVR.

Protein excretion decreased significantly in subjects who achieved SVR [mean difference, 1.04 g/24 h; (95% CI 0.20–1.89, P ¼ 0.02)];

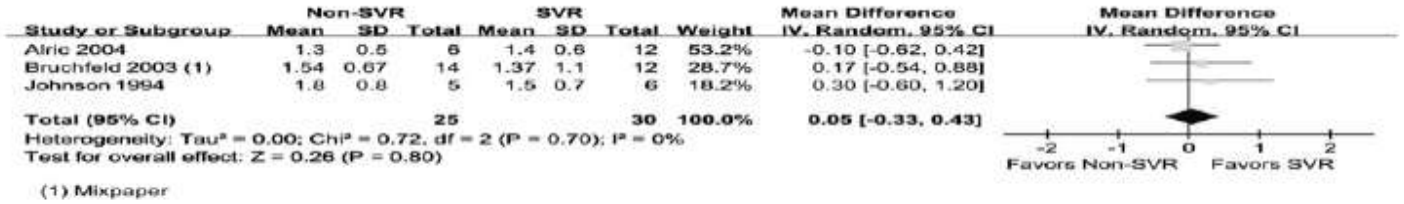

Fig. 5. Forest plot of the comparison of blood creatinine evolution between patients with SVR and those with non-SVR.

A significant decrease in blood creatinine was not observed in the SVR group [mean difference, 0.05 mg/dL (95% CI 0.33 to 0.43, P ¼ 0.80)]

Antiviral therapy for HCV-associated glomerulonephritis limitations

- **HCV eradication is obtained in no more than 50% of the patients .**
- **Clinical benefit of antiviral treatment is often transient or restricted to patients with low-grade kidney involvement.**
- The impact of antiviral therapy on long-term kidney disease outcomes remains uncertain.
- Although response to antiviral therapy may take weeks or months, rapidly progressing kidney disease may be present and kidney failure can develop before virus clearance can be obtained.

Exacerbation of Glomerulonephritis in Subjects With Chronic Hepatitis C Virus Infection After Interferon Therapy

Satoshi Ohta, MD, Hitoshi Yokoyama, MD, Takashi Wada, MD, Norihiko Sakai, MD, Miho Shimizu, MD, Tamayo Kato, MD, Kengo Furuichi, MD, Chikako Segawa, MD, Yukimasa Hisada, MD, and Ken-ichi Kobayashi, MD

Rapidly Progressive Glomerulonephritis After Immunotherapy for Cancer

Mark G. Parker, Michael B. Atkins, Angelo A. Ucci, and Andrew S. Levey

M.G. Parker, A.S. Levey, Division of Nephrology, New England Medical Center and the Department of Medicine, Tufts University School of Medicine, Boston, MA

M.B. Atkins, Division of Hematology-Oncology, New England Medical Center and the Department of Medicine, Tufts University School of Medicine, Boston, MA

A.A. Ucci, Department of Pathology, New England Medical Center and Tufts University School of Medicine, Boston, MA

(J. Am. Soc. Nephrol. 1995; 5:1740–1744)

Another case of focal segmental glomerulosclerosis in an acutely uraemic patient following interferon therapy

Sir,

Nephrology Dialysis Transplantation has reported two cases of acute tubular necrosis and nephrotic syndrome following α-Interferon treatment for malignancy. We report another case of acute renal failure and persistent nephrotic syndrome following such therapy. The renal histological lesion was focal segmental glomerulosclerosis (FSGS).

Membranoproliferative Glomerulonephritis in a Patient Treated With Interferon-α for Human Immunodeficiency Virus Infection

Paul L. Kimmel, MD, A. Andrew Abraham, MD, and Terry M. Phillips, DSc

□ CASE REPORT □

Progressive Renal Failure and Blindness Due to Retinal Hemorrhage after Interferon Therapy for Hepatitis C Virus-associated Membranoproliferative Glomerulonephritis

Takayuki SUZUKI, Katsuhiko YONEMURA*, Takehiko MIYAJI**, Hiroyuki SUZUKI**, Reiko TAKAHIRA**, Yoshihide FUJIGAKI**, Taiki FUJIMOTO** and Akira HISHIDA**

Immunosuppressive therapy

Cyclophosphamide

- Before the identification of the strong relationship between mixed cryoglobulinemia and HCV infection, various immunosuppressive agents were used.
- Cyclophosphamide is indicated in HCV-associated glomerulopathies because it is an effective agent for inhibition of B lymphocytes and thus cryoglobulin production.
- Cyclophosphamide has been used successfully in this patient population; however the possibility of flare up of HCV infection and increase in HCV RNA levels should always be kept in mind .

Successful Cyclophosphamide Treatment of Cryoglobulinemic Membranoproliferative Glomerulonephritis Associated With Hepatitis C Virus Infection

Richard J. Quigg, MD, Michel Brathwaite, MD, David F. Gardner, MD,
David R. Gretch, MD, PhD, and Shaun Ruddy, MD

American Journal of Kidney Diseases, Vol 25, No 5 (May), 1995: pp 798-800

Immunosuppressive therapy
Steroids

- High-dose methylprednisolone has been used to treat exacerbations of mixed cryoglobulinaemia for over 30 years .

(Tarantino et al., 1981; De Vecchi et al., 1983).

- Intravenous methylprednisolone pulse therapy did have a dramatic effect on renal function .
- Proteinuria levels were not found to be significantly changed as a result of therapy.
- The basal cryocrit level decreased after pulse therapy

(De Vecchi et al., 1983).

- Rapidly progressive MPGN type 1 with HCV and nephritic syndrome, intravenous pulsed methylprednisolone appeared to be useful in establishing rapid remission but as antiviral therapy was used concurrently it is impossible to ascertain the effect of methylprednisolone alone.

(Ahmed et al., 2008).

Oral steroids

- **Ponticelli and colleagues (1986) reported 27 patients with EMC and acute renal disease who were treated with oral corticosteroids (CCSs) either given alone or in combination with cytotoxic agents .**
- **10 of them (37%) : died or had progressive impairment of renal function**
- **4 patients (15%): renal failure persisted unchanged**
- **13 patients (48%) : improvement of renal function occurred**
- This does not appear to differ markedly from their reporting of the natural outcomes of such patients with supportive treatments alone.

(Ponticelli C, et al 1986)

- **Johnson et al. reported that oral steroids with HCV-associated nephritis had no beneficial effect on kidney function, although it may have improved the purpura.**

(Johnson RJ, et al. Kidney Int 1994; 46: 1704–1700)

The efficacy of oral CCS in influencing the natural outcome of HCV associated nephropathy is unconvincing

- **One problem with steroids and immunosuppressive therapy is the increase in HCV-RNA levels with its possible detrimental consequences on the underlying liver disease .**

(Diamond et al. J Med Virol 1994; 42: و298–294. McHutchison et al. Hepatology. 1993;18:124A. Fong T let al. Gastroenterology. 1994;107:196-199) .

- **A case of fibrosing cholestatic hepatitis (FCH) developed in a previously immunocompetent patient with chronic HCV that was stable until receiving cyclophosphamide and CCS for the treatment of active GN .**

(Saleh F, et al Ann Hepatol. 2007;6:186-189)

- **It has been suggested that, at least in patients with HCV-related renal disease, treatment of acute flares with immunosuppressive therapy is all that is needed for preservation of renal function, while prolonged treatment is of no proven additional benefit.**

(Campise MR, Tarantino A. Glomerulonephritis in mixed cryoglobulinemia: what treatment? Nephrol Dial Transplant. 1999;14:281-283)

Rituximab

Rituximab for the treatment of type II mixed cryoglobulinemia

Sir,

Rituximab is an anti-CD20 human-mouse chimeric monoclonal antibody that has been shown to be effective in the treatment of B-cell low-grade non-Hodgkin's lymphoma (NHL).[1,2] Type II cryoglobulinemia is an immunoglobulin mediated disease of

Francesco Zaja, Domenico Russo, Giovanna Fuga, Francesca Patriarca, Anna Ermacora, Michele Baccarani

Haematologica vol. 84(12):December 1999

Nephrol Dial Transplant (2004) 19: 3054–3061
doi:10.1093/ndt/gfh469
Advance Access publication 19 October 2004

Original Article

Nephrology Dialysis Transplantation

Long-term effects of anti-CD20 monoclonal antibody treatment of cryoglobulinaemic glomerulonephritis

Dario Roccatello[1–3], Simone Baldovino[1,3], Daniela Rossi[1,2], Morteza Mansouri[1,3], Carla Naretto[1,3], Mariella Gennaro[1,3], Roberto Cavallo[1], Mirella Alpa[1], Piera Costanzo[1], Osvaldo Giachino[1], Gianna Mazzucco[4] and Luigi Massimino Sena[1,3]

Rheumatology 2006;45:842–846
Advance Access publication 17 January 2006
doi:10.1093/rheumatology/kel004

Rituximab treatment for glomerulonephritis in HCV-associated mixed cryoglobulinaemia: efficacy and safety in the absence of steroids

L. Quartuccio, G. Soardo[1], G. Romano, F. Zaja[2], C. A. Scott[3], G. De Marchi, M. Fabris, G. Ferraccioli[4] and S. De Vita

Autoimmunity Reviews xxx (2011) xxx–xxx

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Review

Treatment with rituximab in patients with mixed cryoglobulinemia syndrome: Results of multicenter cohort study and review of the literature

C. Ferri [a,*], P. Cacoub [b], C. Mazzaro [c], D. Roccatello [d], P. Scaini [e], M. Sebastiani [a], A. Tavoni [f], A.L. Zignego [g], S. De Vita [h]

Table 1
Demographic and clinico-[illegible] patients treated with rituximab.

Patients no.	87	
M/F	19/68	
Mean age (years ± SD)	62.3 ± 11.4	
Disease duration (years ± SD)	9 ± 6.2	
HCV-associated MC	80	92%
Essential MC	5	6%
MC overlapping with CTD*	2	2%
Cryoglobulin characterization		
Type II	73	84%
Type III	14	16%
Cryocrit (range^)	<0.5 - 26%	
Low C4^	63	72%
Clinical manifestations		
Chronic hepatitis	52	60%
Purpura	51	59%
Renal inv. (MPGN)	38	44%
Peripheral neuropathy	69	79%
Vasculitic skin ulcers	24	28%
B-cell NHL	6	7%
Abdominal vasculitis	1	1%
Main indication to rituximab		
MPGN	26	30%
Skin vasculitis	22	25%
Severe purpura	8	9%
Non-healing ulcers	14	16%
Peripheral neuropathy)	20	23%
B-cell NHL	6	7%
Abdominal vasculitis	1	1%
Multiple symptoms	12	14%

MPGN: membranoproliferative glomerulonephritis.
* CTD: connective tissue diseases.
^ Trace amount of cryoglobulins: cryocrit <0.5%.
^ Undetectable or under lower limit of normal range.

Table 2
Effects of rituximab treatment in 87 patients with active MCs.

		After 6-month from Rituximab cycle		
	Pts no.	CR	PR	NR
Purpura	51	38 (74%)	4 (8%)	9 (18%)
Vasculitic skin ulcers	24	14 (58%)	7 (29%)	3 (12%)
Peripheral neuropathy	69	30 (44%)	18 (26%)	20 (29%)
MPGN	38	19 (50%)	17 (45%)	2 (5%)
NHL-B	6	3 (50%)	2 (33%)	1 (17%)
Abdominal vasculitis	1	1 (100%)	0	0
Cryocrit	87	26 (30%)	17 (19%)	44 (51%)
Low C4	63^	18 (29%)	13 (21%)	32 (50%)

*Adverse events**	
Total	18 (21%)
Infusion-related reactions	4 (5%)^
Infections	4 (5%)**
Mild adverse events	8 (9%)^^
Worsening of MC syndrome	2 (2%)^^
Drop out due to adverse events	4 (5%)§

CR: complete response; PR: partial response; NR: non-responders.
NHL-B: Non-Hodgkin's B-cell lymphoma.
^ Undetectable or under lower limit of normal range.
* Severe adverse events 3 pts: serum sickness-like reaction, infectious pneumonia, gangrene.
^ Infusion-related reactions: hypotension (2), urticaria (1), serum sickness-like reaction (1).
** Infections: urinary tract infection (2), infectious pneumonia (1), gangrene (1).
^^ Worsening of severe skin vasculitis (1 pt) or peripheral neuropathy (1 pt).
^^ Mild manifestations: neutropenia (2), hypogammaglobulinemia (5), hypertransaminasemia(1).
§ Drop out: worsening of vasculitis (1), serum sickness-like reaction (1), severe infections (2).

Autoimmunity Reviews xxx (2011) xxx–xxx

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Review

Treatment with rituximab in patients with mixed cryoglobulinemia syndrome: Results of multicenter cohort study and review of the literature

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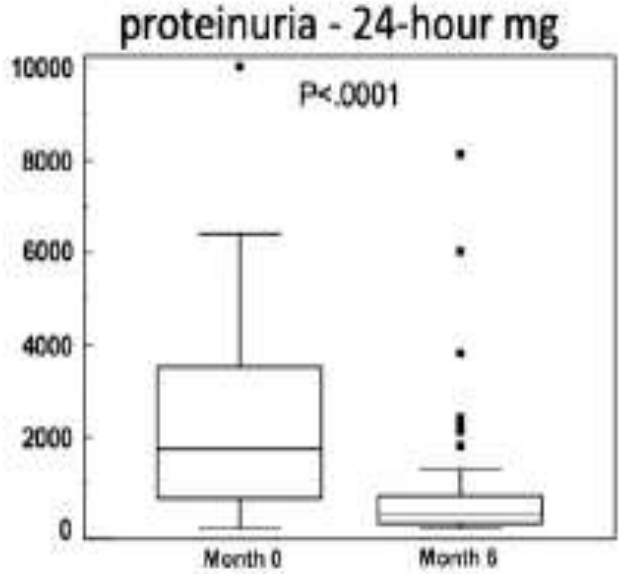

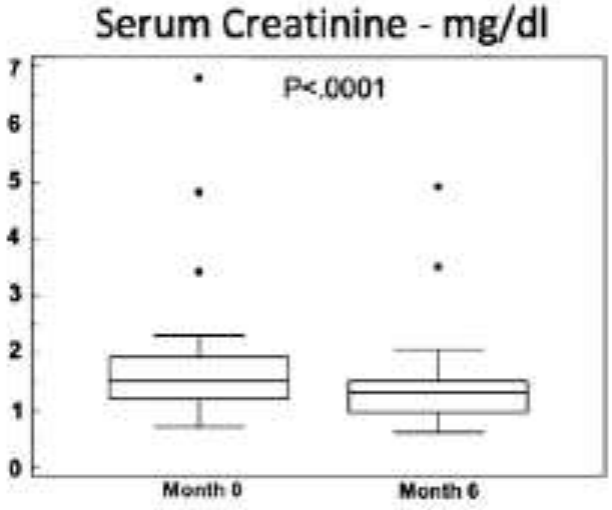

24-hour proteinuria (from2.2±2.1SD to 0.9±1.7SD g/24 h, (p≤.0001),

Significant decrease of serum creatinine (from 1.8±1.1SD to 1.4± 0.8SDmg/dl; p≤.0001),

Anti-CD20 monoclonal antibody (rituximab) treatment for cryoglobulinemic vasculitis: where do we stand?

P Cacoub, A Delluc, D Saadoun, D A Landau, D

Ann Rheum Dis 2008;**67**:283–287. doi:10.1136/ard.2006.065565

Table 1 Main baseline characteristics of patients with cryoglobulinemia vasculitis who received anti-CD20 antibody (rituximab) treatment

	No. of patients with available data	No. of positive patients	Positive patients (%)
Age (years), mean (range),	57	–	[illegible]
Sex (f)%	57	45	79
Vasculitis :			
Duration (months), mean (range)	57	–	60.1 (6–240)
Skin involvement	57	48	84.2
Arthralgia	57	35	61.4
Neuropathy	57	31	[illegible]
Glomerulonephritis	57	18	31.6
Immunology:			
Cryoglobulin positive	57	57	100
Type I		2	3.5
Type II		41	71.9
Type III		10	17.6
Type unknown		4	7.0
Rheumatoid factor positive	57	30	52.6
C4 serum level (mg/dl), mean	57	–	7.1
HCV status	57		
HCV RNA negative or unknown		14	24.6
HCV RNA positive		43	75.4
Genotype 1–4		24	55.8
Genotype 2–3		18	41.9
Genotype not available		1	2.3
Viral load >2 million IU/mL	8	6	75.0
ALT (IU/L), mean	31	–	54.3
Previous treatment			
HCV infection	37		
Interferon α		27	72.8
Pegylated interferon α plus ribavirin		4	14.8
None		12	32.4
Vasculitis treatment:			
Corticosteroids	36*	31	86.1
Immunosupressive drug	56	18	32.1
Plasma exchange	56	12	21.4

Table 2 Main course of cryoglobulinemia vasculitis features after anti-CD20 antibody (rituximab) infusion

	No. of patients positive at baseline	No. of patients with available data at follow up	Patients with available data at follow up (%)
Vasculitis:			
Skin involvement	48	40	
CR	–	27	67.5
PR	–	5	12.5
NR	–	8	20.0
Arthralgia	35	34	
CR	–	18	52.9
PR	–	9	26.5
NR	–	7	20.6
Neuropathy	31	29	
CR	–	9	31.0
PR	–	18	62.1
NR	–	2	6.9
Glomerulonephritis	18	18	
CR	–	12	66.6
PR	–	3	16.7
NR	–	3	16.7
Cryoglobulin	57	22*	
CR	–	16	72.7
PR	–	2	9.1
NR	–	4	18.2
Follow up after rituximab therapy:			
Duration (months), mean (range)	57	56	9.7 (0.3–24)
Relapses	–	14 out of 36	39

*The serum cryoglobulin status at the end of follow-up was available in 22 patients.
CR, complete response; NR, non-response; PR, partial response.

ARTHRITIS & RHEUMATISM
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A Randomized Controlled Trial of Rituximab for the Treatment of Severe Cryoglobulinemic Vasculitis

S. De Vita,[1] L. Quartuccio,[1] M. Isola,[2] C. Mazzaro,[3] P. Scaini,[4] M. Lenzi,[5] M. Campanini,[6]

ARTHRITIS & RHEUMATISM
Vol. 64, No. 3, March 2012, pp 835–842
DOI 10.1002/art.34322

A Randomized Controlled Trial of Rituximab Following Failure of Antiviral Therapy for Hepatitis C Virus–Associated Cryoglobulinemic Vasculitis

Michael C. Sneller,[1] Zonghui Hu,[1] and Carol A. Langford[2]

ARTHRITIS & RHEUMATISM
Vol. 64, No. 3, March 2012, pp 843–853
DOI 10.1002/art.34331

A Randomized Controlled Trial of Rituximab for the Treatment of Severe Cryoglobulinemic Vasculitis

S. De Vita,[1] L. Quartuccio,[1] M. Isola,[2] C. Mazzaro,[3] P. Scaini,[4] M. Lenzi,[5] M. Campanini,[6]

Table 1. Characteristics of the patients who were randomized into the study, by treatment group*

	All patients (n = 57)	Non-RTX group (n = 29)	RTX group (n = 28)
Age, mean ± SD years	63.27 ± 10.78	63.0 ± 10.6	62.85 ± 11.36
Sex, no. female/male	46/11	22/7	24/4
No. HCV positive/no. tested	53/57	28/29	25/28
Antiviral therapy failure/not indicated	28/25	14/14	14/11
BVAS at baseline, mean ± SD	10.51 ± 4.49	9.55 ± 3.64	11.89 ± 5.42
No. with skin ulcers	7	2	5
No. with nephritis	17	10	7
No. with neuropathy	33	17	16
Rheumatoid factor, mean ± SD IU/ml	528.55 ± 840.12	556.58 ± 784.04	501.38 ± 891.81
C4, mean ± SD mg/dl	6.62 ± 8.05	6.81 ± 7.37	6.27 ± 8.7

* There were no significant differences between the two treatment groups. RTX = rituximab; HCV = hepatitis C virus; BVAS = Birmingham Vasculitis Activity Score.

Table 3. Improvement during the first two months of the study*

	Non-RTX group			RTX group		
	Baseline	Month 1	Month 2	Baseline	Month 1	Month 2
Skin ulcers						
No. of ulcers	2.5 (1–4)	2.5 (1–4)	4.0 (1–7)	2.0 (1–10)	2.0 (1–5)	0 (0–2)
Diameter, cm	2.5 (1–4)	2.5 (1–4)	2.5 (2–3)	5.0 (2–7)	4.0 (1–6)	0 (0–3)
Glomerulonephritis						
Serum creatinine, mg/dl	1.2 (0.7–2.3)	1.2 (1.0–2.0)	1.5 (0.8–2.4)	1.6 (0.7–2.8)	1.2 (0.8–6.0)	1.6 (0.8–6)
Proteinuria, gm/24 hours	2.0 (0.9–6.8)	2.1 (0.9–7.0)	1.85 (1.0–11.0)	2.0 (0.6–7.9)	0.6 (0.5–7.8)	0.9 (0.5–4.5)
Active urinary sediment	8/10	7/9	9/9	6/7	5/7	5/7†
Peripheral neuropathy‡						
VAS score for pain	88 (30–100)	80 (20–100)	90 (0–100)	70 (10–100)	52 (0–100)†	40 (0–81)§
VAS score for paresthesias	90 (10–100)	70 (10–100)	80.5 (0–100)	89 (30–100)	63 (30–100)	44 (10–100)
Any grade of improvement vs. baseline¶						
Skin ulcers	-	0/2	1/2	-	3/5	5/5
Glomerulonephritis	-	2/9	1/9	-	4/7	5/7
Peripheral neuropathy	-	4/17	10/14	-	6/15	12/14
Total	-	6/28	12/25	-	13/27†	22/26†

- The primary end point :Survival of treatment at 12 months (i.e., the proportion of patients who continued taking their initial therapy), was statistically higher in the RTX group (64.3% versus 3.5% [$P <$ 0.0001 .
- Glomerulonephritis: 7 patients in the RTX group who had glomerulonephritis, 2 showed a complete response, 2 showed a partial response, and 3 showed treatment failure at 6 months.
- The findings of this trial demonstrate the superiority of RTX monotherapy as compared to conventional therapy with Cs, AzA, cyclo, or plasmapheresis

Rituximab

- **Caution is needed for several reasons:**
- **1- No control trials are available.**
- **2-All data come from small series or case reports.**
- **3- Most cases have reported only a short-term follow-up Thus, further assessment of the longterm effects of prolonged B-cell depletion is still required .**
- **4-In a large number of cases there were insufficient data, particularly regarding the course of HCV viral load and liver enzymes .**

Cacoub P, Ann Rheum Dis. 2008;67:283-287- 94. Ahmed MS, Wong CF.. 2007;20:350-356.

- **5-Several reports of fatal fulminating hepatitis**

(Sarrecchia C, J Infect Chemother. 2005;11:189-191-, Perceau G et al .. Br J Dermatol. 2006;155:1053-1056. Lake-Bakaar G, et al.,Blood. 2007;109:845-846. 100, Ennishi D, Am J Hematol. 2007;83:59-62, Vento S, et al. Lancet. 1996;107:196-199).

ARTHRITIS & RHEUMATISM
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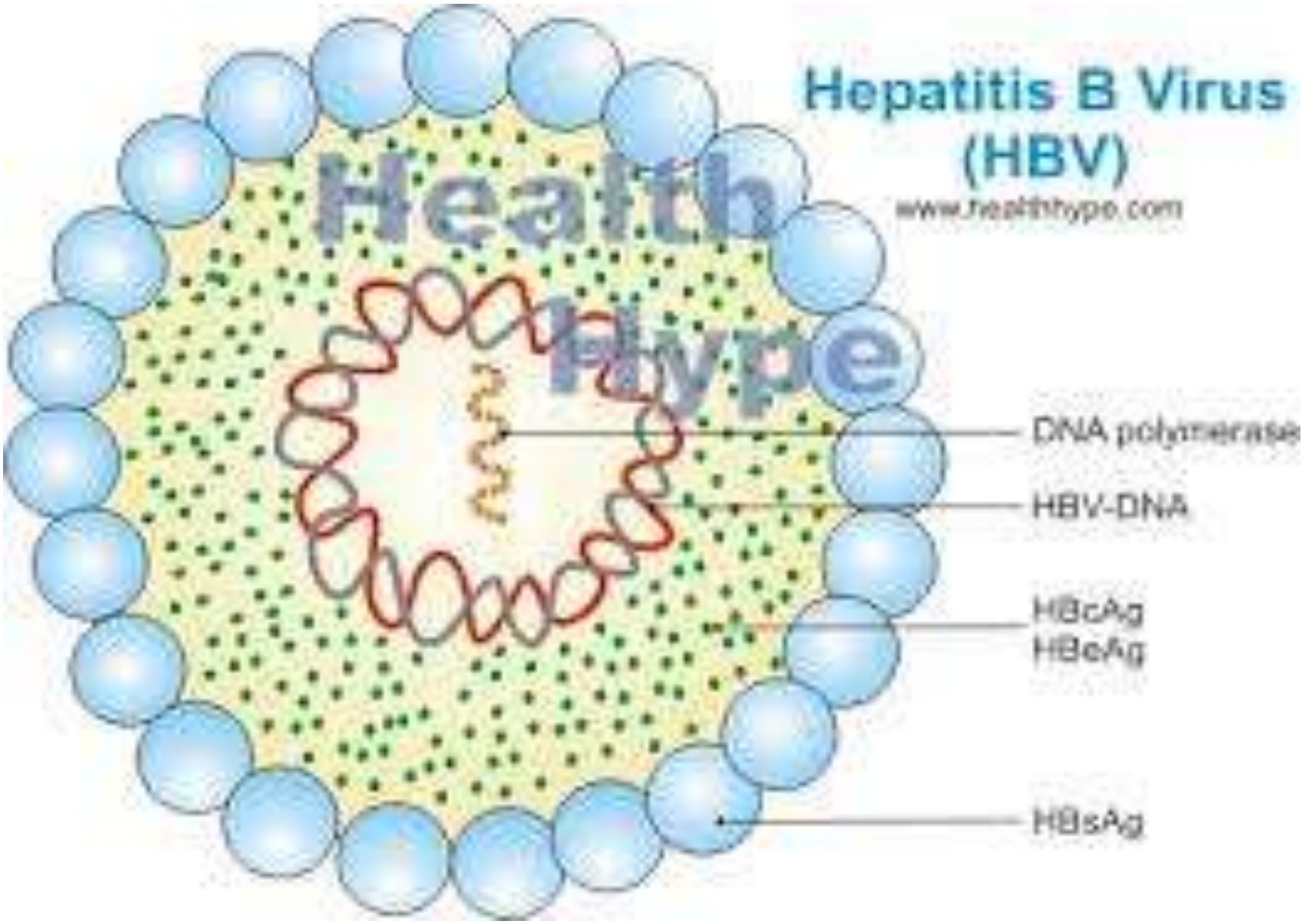
Rituximab May Form a Complex With IgMκ Mixed Cryoglobulin and Induce Severe Systemic Reactions in Patients With Hepatitis C Virus–Induced Vasculitis

Damien Sène, Pascale Ghillani-Dalbin, Zahir Amoura, Lucile Musset, and Patrice Cacoub


Hepatitis B Virus
(HBV)
www.healthhype.com
Health
Hype
DNA polymerase
HBV-DNA
HBcAg
HBeAg
HBsAg

- **In 1971, Combes et al. were the first to describe a 53-year-old man with membranous glomerulonephritis due to glomerular deposition of Australian-antigen-containing immune complexes.**

  (Combes B, et al., Lancet 1971;ii:234–237).

- **The three most common types of renal disease resulting from HBV infection are:**

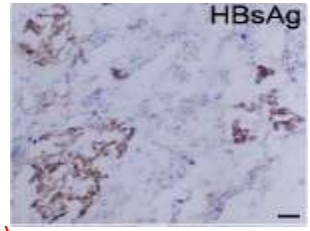
- **●Membranous glomerulonephritis**

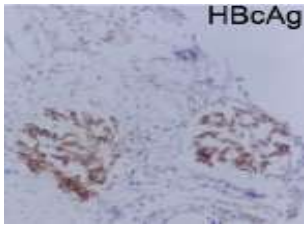
- **●Membranoproliferative glomerulonephritis (MPGN)**

- **●Polyarteritis nodosa (PAN)**
- **In addition,**
- **Mesangial proliferative glomerulonephritis,**
- **IgA nephropathy,**
- **Amyloidosis.**

Pathogenesis

- **1-Deposition of immune complexes of hepatitis B antigen-antibody complexes .**
- **HBsAg .**
- **HBcAg.**
- **HBeAg .**





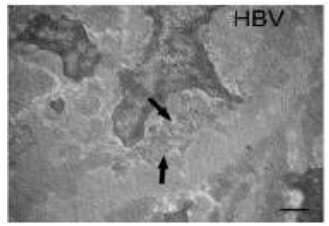
(Hirose H e tal : Kidney Int 1984;26:338–341, Ito H: Lab Invest 1981;44:214–220).

- **2- Secondary liver disease in genetically predisposed individuals Increased production of circulating mediators (such as tumor necrosis factor, interferons, IL-8, and/or other factors) may lead to increased glomerular permeability to plasma proteins .**

(Johnson RJ, Kidney Int 1990;37:663–676)

- **The presence of viral antigens in the renal tissue may be coincidental rather than indicative of a causal relationship .**

(Takekoshi Y., Kid Int Suppl 1991 ; 35:S34)



TREATMENT

- The treatment of hepatitis B virus (HBV)-associated renal diseases consists of antiviral therapy in most patients .
- The limited data on the treatment of HBV-associated renal diseases are based upon small case series and uncontrolled observations.
- There are no randomized trials.
- (Conjeevaram HS, Gastroenterology 1995;109:540–546-Abbas NA Nephrol Dial Transplant 1999;14:1272–1275- Wakeel JA, .Am J Kidney Dis 1999;33:1142–1146-Lin CY: Kidney Int 1991;47:225-230).

- This recommendation is based upon observational data .

Antiviral Therapy

- **A retrospective report from the National Institutes of Health (NIH)**
- **15 adults : 10 with MN, 4 (MPGN) , 1 in whom renal biopsy was not available.**
- **IFN alfa 2-b: 5 million units of subcutaneously daily for 16 weeks .**
- **Eight responded (53%) with seroconversion of HBeAg to anti-HBe antibodies and a reduction of HBV DNA to undetectable levels .**
- **In seven patients, this was accompanied by gradual disappearance of proteinuria.**
- **Responders :**

  Had lower baseline HBeAg and HBV DNA levels than nonresponders.

  Remission persisted for a long period after therapy was discontinued.

  Patients with membranoproliferative disease appeared less responsive to treatment.

Conjeevaram HS et al., Gastroenterology 1995 Aug;109(2):540-6.

- **Other studies that examined interferon alfa for HBV-associated renal disease reported sustained seroconversion of HBeAg to anti-HBe in 38 to 80 percent of patients and remission of proteinuria in 25 to 100 percent of patients.**

Lin Cy. Kid Int 1995 , Chung Dr etal, Am J Nephrol 1997.

Kidney International, Vol. 47 (1995), pp. 225–230

Treatment of hepatitis B virus-associated membranous nephropathy with recombinant alpha-interferon

CHING-YUANG LIN

Department of Pediatrics, Veterans General Hospital-Taipei, Taiwan, Republic of China

Table 1. Clinical and laboratory characteristics of HBVMN children in the two groups

	Group 1 ($N = 20$)	Group 2 ($N = 20$)	P
Mean age *years*	6.2 ± 2.4	6.8 ± 2.1	NS
Sex (male/female)	15/5	14/6	NS
Previous length of prednisolone treatment *months*	4.0 ± 1.0	4.1 ± 0.8	NS
Duration of proteinuria *months*	5.2 ± 1.4	5.4 ± 1.8	NS
Magnitude of proteinuria	4.1 ± 0.8	4.0 ± 0.6	NS
Serum Cr *mg/dl*	1.2 ± 0.4	1.1 ± 0.3	NS
Serum albumin *g/dl*	1.9 ± 0.2	2.0 ± 0.2	NS
C_{Cr} *ml/min/1.73 m²*	116.4 ± 7.6	114.9 ± 8.2	NS
Hypertension			
present	0	0	NS
absent	20/20	20/20	NS
Histological grading [a] scores	2.1 ± 0.5 (1–3)	2.0 ± ± .4 (1–3)	NS

[a] The glomerular changes were classified into four stages [22] (stage I to stage IV as grade scores of 1 to 4)

40 HBVMN patients - With HBeAg and HBsAg were positive - in all patients who showed no response to corticosteroid treatment, 20 patients were treated with IFN-· and 20 were given supportive treatment only.

Kidney International, Vol. 47 (1995), pp. 225–230

Treatment of hepatitis B virus-associated membranous nephropathy with recombinant alpha-interferon

CHING-YUANG LIN

Department of Pediatrics, Veterans General Hospital-Taipei, Taiwan, Republic of China

Table 2. Serial changes of hepatitis B markers and proteinuria between two groups of HBVMN patients (N = 20 in each group)

	Before IFNα		After IFNα								Follow-up	
			3 months		6 months		9 months		12 months		24 months	
	Group 2	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
Proteinuria												
>40 mg/M²/hr	20 (100%)	20 (100%)	0	10 (50%)	0	8 (40%)	0	7 (35%)	0	6 (30%)	0	3 (15%)
4-40 mg/M²/hr	0	0	4 (20%)	10 (50%)	2 (10%)	12 (60%)	0	12 (60%)	0	12 (60%)	0 (60%)	10 (65%)
<4 mg/M²/hr	0	0	16 (80%)	0	18 (90%)	0	20[a] (100%)	1[a] (5%)	20[e] (100%)	2[e] (10%)	20[e] (100%)	7[e] (35%)
HBsAg (+)												
HBeAg(+)	20	20	17	20	10	20	8[b]	20[b]	4[d]	20[d]	4[f]	20[f]
HBeAb(+)	(100%)	(100%)	(85%)	(100%)	(50%)	(100%)	(40%)	(100%)	(20%)	(100%)	(20%)	(100%)
HBeAg(+)	0	0	1	0	2	0	2	0	0	0	0	0
HBeAb(+)			(5%)		(10%)		(10%)					
HBeAg(−)	0	0	1	0	8	0	8	0	4	0	5	0
HBeAb(+)			(5%)		(40%)		(40%)		(20%)		(25%)	
HBsAg(−)												
HBe(−)												
HBsAg(−)	0	0	0	0	0	0	2 (10%)	0	4 (20%)	0	0	0
HBsAg(+)	0	0	1 (5%)	0	0	0	0	0	8 (40%)	0	11 (55%)	0
Serum Cr *mg/dl*	1.2 ± 0.4	1.1 ± 0.3	1.2 ± 0.5	1.2 ± 0.3	1.2 ± 0.5	1.2 ± 0.4	1.2 ± 0.5	1.2 ± 0.3	1.2 ± 0.5	1.3 ± 0.4	1.2 ± 0.5	1.4 ± 0.4
C_{Cr} *ml/min/1.73 m²*	116.4 ± 7.6	114.9 ± 8.2	114.2 ± 7.2	110.4 ± 6.4	106.2 ± 6.8	104.2 ± 8.2	101.8 ± 8.1	100.1 ± 7.5	108.4 ± 6.4	98.4	102.4 ± 7.4	89.6 ± 6.3
Elevated ALT	6 (30%)	5 (25%)	0	5 (25%)	0	5 (25%)	0	3 (15%)	0	2 (10%)	0	2 (10%)

Group 1 was the test group with IFNα; Group 2 was control group; Follow-up included both groups after the initial study without IFNα treatment. Both groups previously had prednisolone treatment only.

Comparison between test and control groups was examined by using χ^2 (chi-square) test: [a,e,d,f] $P < 0.01$; [b,c] $P < 0.05$

Response: IFN :At the end of 3 months of treatment, all patients treated with IFN-· were free of proteinuria. In contrast, 20 patients (100%) still have some degree of proteinuria

Virlological response:

IFN group:, 8 patients (40%) had HBeAg seroconversion - HBsAg sero conversion between the 10th and 12th months . (20 %) HBe seroconversion only [HBeAg–/HBsAg+] was found in 4 patients.

Four patients (20%) had no change in HBV serological markers . The remaining 4 (20%) patients had HBeAg–/HBeAb+ HBsAg–/HBsAb– at the end of the 12th month.

In contrast, there was no seroconversion of HBeAg+/HBsAg+ in those treated conservatively.

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BRIEF ARTICLE

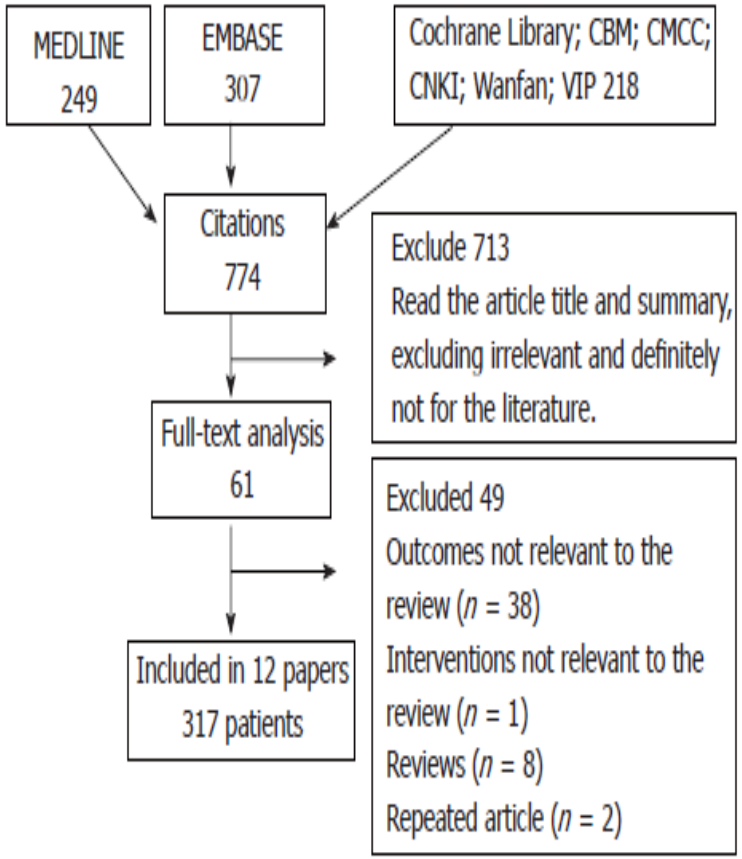
Meta-analysis of combined therapy for adult hepatitis B virus-associated glomerulonephritis

Xiao-Yong Zheng, Ri-Bao Wei, Li Tang, Ping Li, Xiao-Dong Zheng

Table 2 Categories of interventions used in individual studies and duration of follow-up

Ref.	Intervention	Duration	Follow-up	Dropout (*n*)
Fang *et al*[9]	Prednisone 0.8-1.0 mg/kg per day + LAM/ETV/ADV	12 mo	40 mo	0
Cheng *et al*[16]	Prednisolone 0.4 mg/kg per day + MMF + LAM	6 mo	6 mo	0
Dang *et al*[17]	Prednisone 0.8-1.0 mg/kg per day + MMF + LAM	6 mo	6 mo	0
He *et al*[18]	Prednisone 40-60 mg/d + MMF	18 mo	12 mo	0
Liu *et al*[19]	prednisolone 0.5-1.0 mg/kg per day + MMF + LAM	12 mo	12 mo	0
Liu *et al*[20]	Prednisone 1.0 mg/kg per day + ETV	9 mo	9 mo	0
Sun *et al*[21]	Prednisone 0.5 mg/kgper two days + MMF + LAM	12 mo	12 mo	2
Sun *et al*[22]	Prednisone 1.0 mg/kg per day + ADV	6 mo	12 mo	0
Tang *et al*[23]	Prednisone 0.5-0.8 mg/kg per day + MMF	6 mo	12 mo	0
Tang *et al*[24]	Prednisolone 0.4 mg/kg per day + MMF + LAM	6 mo	NA	0
Wu *et al*[25]	Prednisolone 0.4 mg/kg per two days + MMF + LAM	6 mo	12 mo	0
Xia *et al*[26]	Prednisone 0.5 mg/kg per day + LEF +LAM	6 mo	12 mo	0

MMF: Mycophenolate mofetil; LAM: Lamivudine; ETV: Entecavir; ADV: Adefovir dipivoxil; LEF: Leflunomide; IFNα: Interferon α; NA: Not available.



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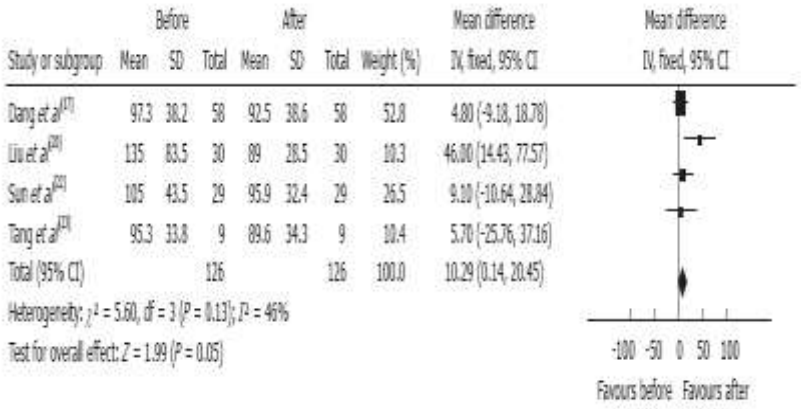

Figure 6 Scr change in combination therapy group. IV: Inverse variance.

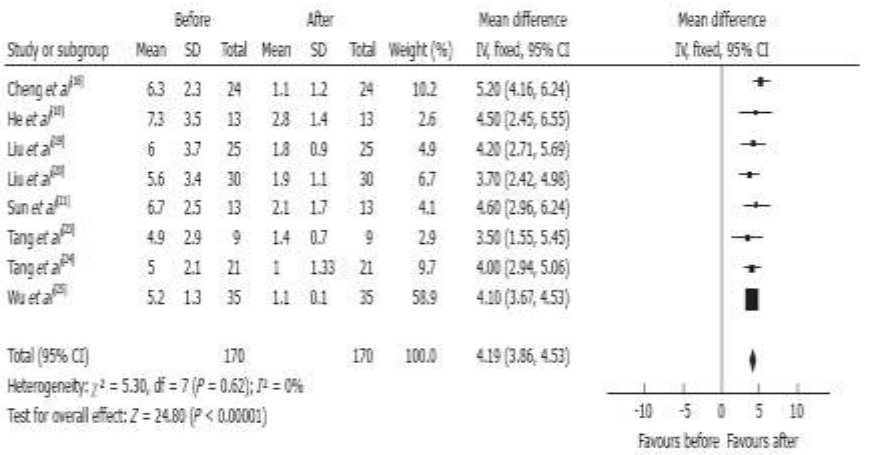

Figure 3 Proteinuria change in steroid combination therapy. IV: Inverse variance.

There was no significant increase in the level of Scr after the treatments.

There was a significant decrease in the level of proteinuria after the treatments (mean difference: 4.19, 95% CI: 3.86-4.53 overall estimated rate for proteinuria remission of 83%.

Corticosteroids

- However, corticosteroids given at the onset of nephrotic syndrome in HBVMN do not seem to have an ameliorative effect on the nephrotic state or lead to clearance of the virus .

(Cadrobbi P et al. Arch Dis Child 1985; 60:583–585).

- Exacerbation of liver impairment has been reported in patients with chronic HBV hepatitis .

(Hoofnagle et al. Ann Intern Med 1986; 104:12–17)

Conclusion

- The interplay between HCV and the kidney is complex.
- In MPGN type I and cryoglobulinemic glomerulonephritis, there is considerable circumstantial evidence for an etiologic link between the viral infection and the renal injury.
- For many of the others, it could be argued that the reported cases represent chance associations of relatively common maladies rather than examples of causal linkage.

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- **Unfortunately, there are no large-scale clinical trials in patients with HCV-associated kidney disease; thus, evidence-based treatment recommendations cannot be made in this patient population.**
- **There is low-quality evidence to recommend treatment of HCV-associated GN. Treatment should be focused on reducing or eliminating HCV replication, and reducing the formation and glomerular deposition of HCV containing immune complexes (including cryoglobulins).**
- **There is very low–quality evidence to suggest that patients with HCV-associated GN and severe kidney manifestations require additional treatment with immunosuppression and/or corticosteroids and/ or plasma exchange.**

9.2: Hepatitis C virus (HCV) infection–related GN

(Please also refer to the published KDIGO Clinical Practice Guidelines for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease.)

9.2.1: For HCV-infected patients with CKD Stages 1 or 2 and GN, we suggest combined antiviral treatment using pegylated interferon and ribavirin as in the general population. (*2C*) [based on KDIGO HCV Recommendation 2.2.1]

9.2.1.1: Titrate ribavirin dose according to patient tolerance and level of renal function. (*Not Graded*)

9.2.2: For HCV-infected patients with CKD Stages 3, 4, or 5 and GN not yet on dialysis, we suggest monotherapy with pegylated interferon, with doses adjusted to the level of kidney function. (*2D*) [based on KDIGO HCV Recommendation 2.2.2]

9.2.3: For patients with HCV and mixed cryoglobulinemia (IgG/IgM) with nephrotic proteinuria or evidence of progressive kidney disease or an acute flare of cryoglobulinemia, we suggest either plasmapheresis, rituximab, or cyclophosphamide, in conjunction with i.v. methylprednisolone, and concomitant antiviral therapy. (*2D*)

KDIGO Clinical Practice Guideline for Glomerulonephritis
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9.3: Hepatitis B virus (HBV) infection–related GN

9.3.1: We recommend that patients with HBV infection and GN receive treatment with interferon-α or with nucleoside analogues as recommended for the general population by standard clinical practice guidelines for HBV infection (see Table 23). (*1C*)

9.3.2: We recommend that the dosing of these antiviral agents be adjusted to the degree of kidney function. (*1C*)

Thank you

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Hepatitis C virus-induced vasculitis: therapeutic options

Patrice Cacoub,[1,2,3,4] Benjamin Terrier,[5] David Saadoun[1,2,3,4]